

### REMARKS

Upon entry of the amendments herein, claims 22-26, 28, 29, 31-33 and 35-40 remain pending in the application. Claim 22 has been amended, and claim 30 has been cancelled. No new matter has been introduced by any of the amendments. The cancellation of claim 30 herein is made without prejudice.

#### I. Introduction

Applicants and the undersigned acknowledge with gratitude Examiner Borin's time and input during the interview in Alexandria on February 23, 2005 to discuss the outstanding issues. The amendments and remarks below reflect what was discussed during the interview. Also, as required in the Interview Summary issued following the interview, this communication includes throughout a recounting of the substance of the interview.

Claim 30 has been withdrawn by the Examiner on the grounds that it is directed to a nonelected invention. Applicants disagree. The concept of Variance recited in claim 30 was present in the claims as originally filed. Original claim 30 ultimately depended from claim 22 and further recited the use of Variance in the design. Claim 30 has nevertheless been cancelled without prejudice or disclaimer in the interest of

expediting prosecution of the application. Applicants maintain the right to resume prosecution of the subject matter of this claim in a continuation application.

During the interview, Professor Ned Wingreen carefully explained the substance of the invention. In particular, Professor Wingreen clarified the distinction between amino acid sequences per se, which the Examiner has seized on in rejecting the claims, and the configurations or folds that are achieved for the first time by the claimed invention. Much of the substance of this explanation can be found in the published article of Li, et al., Science 273, 666-669 (1996), a copy of which is provided herewith for the Examiner's information as part of the accompanying Information Disclosure Statement. In particular, Applicants point out the Li disclosure on page 667, second column, first full paragraph. More generally, one of skill in the art reading and understanding the Li, et al. article can appreciate that the instant specification adequately supports the claimed invention and that the language of the claims adequately describes the invention.

Professor Wingreen explained to the Examiner that the backbone configurations identified according to an aspect of the invention are separate and distinct from actual sequences of amino acids. He also explained how the space-filling units

(spheres and other space-filling generic side chains) assigned to each configuration are in the positions that amino acid residues would occupy in a protein or polypeptide with the same backbone configuration. Accordingly, there is a one-to-one correlation between the space-filling units assigned to the backbone configuration and the amino acid residues that are in those positions once a protein adopting the configuration has been synthesized.

The Examiner acknowledged that Professor Wingreen's explanation improved his understanding of the concept of the invention as claimed. It is Applicants' understanding that many, at least, of the claim-language issues have been resolved. Nonetheless, certain issues are further addressed below.

## II. Acknowledgment of References

Applicants note the Examiner's acknowledgment of receipt of the Information Disclosure Statement filed with the previous response and the Examiner's indication that "the cited references have been considered."

## III. Written Description Rejections under 35 U.S.C. § 112, 1<sup>st</sup> Paragraph

Claims 22-26, 28, 29, 31-33 and 35-40 have been rejected under 35 U.S.C. §112, first paragraph as not conforming with the written description requirement. In particular, the Examiner has singled out some instances of language added in Applicants' previous response that allegedly introduce new matter. These issues were not discussed at the interview.

The Examiner cites as new matter Applicants' addition of the word "fixed" so that the generating step of claim 22 recites "configurations of fixed length...." The Examiner apparently supposes that this language requires a specific value of length that is not disclosed in the specification. This reading of the amendment is incorrect. Rather, the amendment merely conveys clearly what is supported by disclosure in the specification, namely, that one starts the design process by settling on a particular length of desired, novel configuration. The length can be chosen as any that is desirable. All configurations generated for a particular analysis are of that "fixed" length. Although this explanation is sufficient to further prosecution, Applicants have also replaced the phrase "fixed length" with the phrase "a preselected length."

The phrase "another space-filling generic side chain" has also been cited as introducing new matter. One of ordinary skill in the art would readily understand not only that other

shapes besides spheres could be used in the analysis but what those shapes might be. As a courtesy to the Examiner, Applicants have provided herewith via the accompanying Information Disclosure Statement a copy of the article of Fogolari et al., Biophysical Journal 70, 1183-1197 (1996), which provides an idea of the state of understanding in the field and support for Applicants' contention that the language in question does not constitute new matter. This understanding is summarized in the first paragraph of page 1188 of the reference.

At the very least, then, workers in the field were aware that any suitable nonspherical shape, e.g. an ellipsoid, can also be used as a space-filler in the instant invention. Rather than categorically list all possibilities, Applicants have properly claimed a genus of space-fillers.

And, similar to the case wherein a sphere is used, one of skill in the art would appreciate that the values of "fixed" or "preselected" axes (semi-major and semi-minor), e.g., of an ellipsoid can be determined using the same criteria as are used in determining the "fixed" or "preselected" value of the radius of a sphere. [See Applicants' response in the first paragraph of Section IV below to the Examiner's allegation that the phrase "fixed radius" with respect to spheres is unclear.]

The Examiner asserts that the phrase "evaluating the surface exposure of...generic side chain" also constitutes addition of new matter. For the same reason that one of skill in the art would understand that a generic space-filling side chain could be substituted for a sphere in the analysis, one would understand that the analysis of surface exposure of such a side chain could be achieved in the same way as the surface exposure evaluation for a sphere. Accordingly, this claim amendment does not constitute new matter either.

#### IV. Rejections under 35 U.S.C. §112, 2<sup>nd</sup> Paragraph

The claims have also been rejected under 35 U.S.C. §112, second paragraph as being indefinite. In the first place, the Examiner asserts that the phrase "fixed radius" with respect to a sphere is not clear. However, again, Applicants did not amend the claim language to convey that the radius had to be of some precise value that is not disclosed in the specification. As the Examiner acknowledges, there is disclosure on page 8 that teaches how to determine the desired radius. Applicants respond to the Examiner's queries about what a "natural backbone configuration" is and how it is selected as follows: Once the determination is made for a particular analysis, i.e., what the largest radius is for which a representative set of natural

backbone configurations obtained from the Protein Data Bank (PDB) are not self-intersecting, the radius for all spheres is "fixed" or set to that value; this is the meaning of the introduced language (as well as the specification disclosure), and there is no ambiguity as to its meaning. A "natural backbone configuration" is a known, naturally occurring protein fold, one which can be found in the PDB.

The introduction of the language "another space-filling generic sign chain" is also an alleged basis for rejecting claim 22 and claims dependent therefrom as indefinite. The same arguments that, above, overcome the written-description-requirement rejection in connection with this phrase apply equally here. One of skill in the art would understand that alternate shapes can be used and what those shapes might be. The Examiner is again referred to the Fogolari article provided herewith.

Similarly, then, one would apply the same method for evaluating the surface exposure of a sphere to the more general evaluation of such exposure of a generic side chain.

The Examiner further asserts that the phrase "generating sequences of hydrophobicities" in claim 22 is unclear. At the time the Examiner leveled this rejection, he was apparently unable to reconcile the populating of the backbone with spheres

or other space-filling generic side chains with the reference to hydrophobicities of individual amino acids. It must be appreciated that the use of the phrase "amino acids" in this context is a shorthand readily understood by one of skill in the art. As is clear from the specification and claims and as was further explained to the Examiner during the interview, the design tool itself according to the present invention emphatically does not involve the use of specific amino acids and amino-acid side chains. Rather, the individual units, i.e., the spheres and/or generic side chains that make up a configuration selected as designable are in positions that amino acid residues would occupy in a protein or polypeptide that might subsequently be synthesized and would have the selected configuration.

In the same rejection, the Examiner also questions the meaning of such terms as "allowed sequences," "uniform weight" and "random" generation of sequences of hydrophobicities. In the first place, this language is no longer found in the rejected claims and using the terms as bases for asserting that the claims are unclear is unjustified. The language to which the Examiner refers was replaced by alternative language, also derivable from this application. Furthermore, as explained during the interview, and as reiterated in summary above, the



candidate sequences modeled according to the present invention are distinct from actual sequences of amino acids.

It should now be clear that the answer to, for example, the Examiner's query in the Office Action as to whether the recited sequences of hydrobilities are "completely random and unrelated to any preceding step" is definitely "yes." Applicants reiterate that there are no specific amino acids or side chains thereof introduced in the steps preceding the "generating" step, and such amino acids and side chains are not required by the claimed method for designing realizable protein folds. This has been further clarified by amendment of the "assigning" step of claim 22. Again, the pending claims relate to the identification of novel but designable protein folds.

The Examiner also questions what is meant in describing the "determining" step of claim 22. Applicants believe, based on feedback from the Examiner in the interview, that the explanation provided by Professor Wingreen at that time addressed and resolved this issue and generally resulted in clearer understanding of the claimed invention.

The Examiner also believes that the recitation in the recording step of claim 22 that each sequence is involved is in conflict with disclosure on page 10 of the specification that it is not necessary to find the ground-state configuration for all

sequences. The claim has been amended to more particularly point out that only each sequence of the particular subset that is arrived at through the preceding steps is to be analyzed, not each sequence that was possible when the process was begun.

V. Enablement Rejections under 35 U.S.C. §112, 1<sup>st</sup> Paragraph

The claims have also been rejected under 35 U.S.C. §112, first paragraph as being nonenabled. These rejections are based on the same terms previously singled out in other rejections, e.g., "fixed length," "fixed radius," and "another space-filling generic side chain" or are based on other issues raised by the Examiner in connection with other rejections addressed above in Sections III and IV. The explanations given before of the meaning and acceptability of these phrases and the inappropriateness of the issues raised apply to this rejection as well. Furthermore, as also explained above, one of skill in the art would understand what is meant by a "natural backbone configuration" and appreciate that the steps subsequent to assigning "another space-filling generic side chain" to a position could be performed in the same way as for assignment of a sphere.

The study described in the accompanying Wingreen Declaration, performed using the disclosed and claimed design method, and the results obtained thereby provide answers to the

issues raised by the Examiner and demonstrate beyond question that the method is fully enabled.

VI. Rejections under 35 U.S.C. §101/§112, 1<sup>st</sup> Paragraph

The claims remain rejected under 35 U.S.C. §101 as being directed to a nonstatutory invention and under 35 U.S.C. §101/§112, first paragraph on the grounds that the claimed design method does not have a substantial or well-established utility. The rejection all but ignored the arguments made by Applicants in their last response, while the Examiner conceded in the Office Action that "the method produces amino acid sequences...." In fact, as explained to the Examiner during the interview, as the Examiner indicated he understood, and as can be understood from the plain language of the claims, the products of the method according to the present invention are not per se polypeptides with specific amino acid sequences, but are designable backbone configurations which constitute particularly desirable new folds that can be utilized in the production of new and useful proteins. As set forth in the accompanying Declaration of Professor Wingreen, "real world" benefit has been obtained by eliminating undesignable configurations, indisputably saving a vast amount of labor. That this is a real world benefit is equally beyond dispute.

[See Wingreen Declaration, page 2.] It is not required that actual "real world" proteins have been produced to confer patentability on the claimed invention; requiring this impermissibly ignores the language of the claims and Applicants' arguments and evidence.

The Examiner has failed to address, much less rebut, Applicants' arguments that the claimed invention would be considered by any normal and accepted criteria to be useful solely on the basis of the fact that it provides means by which vast amounts of time, labor and resulting cost can be saved simply by eliminating new configurations that could not be the stable ground state of any sequence and so would be of no use whatsoever. The specific and substantial utility of the claimed invention is disclosed in the specification on, for example, page 4, lines 12-19 and page 4, lines 29-31. The Examiner has failed to meet his burden of proving that a claimed design tool that affords demonstrable labor-saving lacks utility.

In maintaining this rejection, the Examiner has cited MPEP §2107.01. However, while the material quoted by the Examiner may have bearing outside the context of the present invention, it does not provide a basis for the present rejection. The *Substantial Utility* section of MPEP §2107.01 enumerates some examples of situations wherein a "substantial utility" is not

defined. Example (A), cited by the Examiner, arises when there is a requirement for "Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved." [Emphasis added.] Again, the claims are directed not to a product requiring research, but to a computer-implemented design method. The design method itself, as abundantly shown above and in the accompanying Declaration of Professor Wingreen, is self-evidently useful and has been demonstrated to be labor saving, as well as to yield novel, designable protein folds.

Further along these lines, the Examiner has again invoked Shakhnovich, alleging that the cited passage therein demonstrates that "identifying use of the claimed method of polypeptide design would require carrying out further research." The Examiner has repeated virtually verbatim the reference to Shakhnovich from the previous Office Action and has chosen not to comment at all on Applicants' remarks in their last response regarding the inappropriateness of Shakhnovich to the analysis of patentability in the present case. While the Examiner has cited Shakhnovich's reference to the possibility of "a relatively low synergy between experiment and theory," he (the Examiner) has not mentioned, for example, the very next sentence in the cited Shakhnovich passage in which reference is made to

"[A]n important success story based on such synergism of theory and experiment...." In any event, as should be recognized by the Examiner, successful practice of the claimed invention does not itself require further research. The determination of the activity properties of proteins having the identified configurations is a matter for a completely different study carried out subsequently to the practice of the claimed invention.

The Examiner also cited example (C) under the *Substantial Utility* section of MPEP §2107.01: "A method of assaying for or identifying a material that itself has no specific and/or substantial utility." This example is derived from such cases as *Brenner V. Manson*, 148 USPQ 689, (1966). Brenner is inapposite and not controlling in this case. Cases such as Brenner dealt with claims to a composition of matter that had no known use or to chemical processes for producing actual known compositions of matter admittedly having no known use, not with computer-aided methods for designing proteins with realizable backbone configurations and eliminating nondesignable configuration candidates.

The identification or selection of configurations via the claimed design method is not the empirical "identifying" of an actual material as referred to in example (C). To the contrary

the claimed method confers, among other advantages, an ability to eliminate countless unsuitable permutations and the exorbitant labor and expense their elimination would require in the absence of the claimed invention. This advantage is more than sufficient to impart the required utility to the claimed subject matter.

While Brenner is plainly not on point, other authority relating to computer-implemented inventions is controlling and makes clear that the claimed invention satisfies 35 U.S.C. §101 and the written description prong of 35 U.S.C. §112, 1<sup>st</sup> paragraph.

The Examiner's attention is directed to the following passages from the MPEP guidelines on utility:

1) As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. [MPEP §2107.02 III.A]

2) Deficiencies under the 'useful invention' requirement of 35 U.S.C. 101 will arise in one of two forms. The first is where it is not apparent why the invention is 'useful.' This can occur when an applicant fails to identify any specific and substantial utility for the invention or fails to disclose enough information about the

invention to make its usefulness immediately apparent to those familiar with the technological field of the invention.... The second type of deficiency arises in the rare instance where an assertion of specific and substantial utility for the invention made by an applicant is not credible. [MPEP §2107.01-General Principles Governing Utility Rejections.]

The Examiner has failed to carry his burden under these rules.

Applicants have easily met the criteria of clearly disclosing the utility of the instantly claimed design method and that such disclosure is eminently credible to one of skill in the art. There is no basis for this rejection, and it should be withdrawn.

During the interview, the Examiner indicated that providing an example of a protein or polypeptide that could be designed using the claimed method would be treated as evidence of utility to satisfy 35 U.S.C. §101. Although Applicants do not acquiesce in any such requirement, given the subject matter being claimed (noting that there simply is no synthesis step in the claimed design method, nor is one required), they have provided in the accompanying Declaration data showing the production of just such an example.



These data are provided in the form of a Declaration signed by Dr. Ned Wingreen, one of the named inventors and the Applicant present at the interview. As explained by Dr. Wingreen in the Declaration, these data demonstrate the production of a polypeptide with folding properties on a par with those that would be observed in a naturally occurring molecule. [See Wingreen Declaration, pages 5-7, including Figures 3-5.] Thus, one of skill in the art would find assertions of the potential utility of such a new protein structure to be credible, underscoring the utility of the claimed design method that led to the protein. Further demonstrating the immediate utility and as set forth by Dr. Wingreen in the Declaration, the study described therein also enabled the elimination of innumerable configurations which would be unsuitable no matter what amino acid residues were inserted, saving vast amounts of costly labor and other resources. [Declaration, page 2.]

During the interview, the Examiner also suggested adding a protein synthesis step to the claimed design method as a partial response to the allegation that there is presently no "real world" utility. However, again, it must be emphasized that the immediate utility does not lie in the production of proteins themselves and that it is improper to require Applicants to

provide a "working example" of a protein that might arise out of the design/identification of a desirable backbone configuration. This would be akin to requiring the inventors of a new type of hammer to furnish examples of objects the hammer was used to make, plainly in derogation of controlling legal authority. Nevertheless, Claim 22 has been amended with the issue of utility in mind, but only to more particularly point out the nature of the claimed invention as a resource-saving, design tool.

Also touched on during the interview was the issue of prior art. This subject was broached by Applicants even though the previous prior art rejection had been tabled by the Examiner. The Examiner indicated that he was not prepared to discuss the details of that rejection until, in effect, he better understood the claimed subject matter.

As all of the outstanding claim-language issues have been sufficiently addressed in this response, Applicants respectfully urge the Examiner to withdraw these rejections and to act on any prior art issues, if any, so that prosecution will no longer be subject to the delays of piecemeal examination.

VII. Conclusion

To reiterate, Applicants have fully addressed all of the claim issues under 35 U.S.C. §§112 and 101 and have submitted the Wingreen Declaration in support of their position. Applicants therefore respectfully request that these rejections be withdrawn and that the Examiner raise prior art issues, if any, that may bear consideration.

The Commissioner is hereby authorized to charge any additional fees which may be due in connection with this communication to Deposit Account No. 23-1703.

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Respectfully submitted,



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Enclosures